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Hyperspectral imaging and characterization of allergic contact dermatitis in the short-wave infrared

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Abstract

Short-wave infrared hyperspectral imaging is applied to diagnose and monitor a case of allergic contact dermatitis (ACD) due to poison ivy exposure in one subject. This approach directly demonstrates increased tissue fluid content in ACD lesional skin with a spectral signature that matches the spectral signature of intradermally injected normal saline. The best contrast between the affected and unaffected skin is achieved through a selection of specific wavelengths at 1070, 1340 and 1605 nm and combining them in a pseudo-red-green-blue color space. An image derived from these wavelengths normalized to unaffected skin defines a “tissue fluid index” that may aid in the quantitative diagnosis and monitoring of ACD. Further clinical testing of this promising approach towards disease detection and monitoring with tissue fluid content quantification is warranted.

Graphical Abstract

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AUTHOR CONTRIBUTIONS

Tommy Du, Deependra K. Mishra, Andy Yu, Helena Hurbon and Steven T. Wang were involved in investigation, programming, hardware design and data collection, Leonid Shmuylovich was involved in conceptualization, data analysis, results discussion, writing—original draft; Mikhail Y. Berezin was involved in conceptualization, writing—original draft, project management.

CONFLICT OF INTEREST

M.B. is the founder of HSpEQ LLC, a hyperspectral imaging software company.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Color visible camera

SWIR-HSI



Keywords

allergic contact dermatitis; hyperspectral imaging; optical imaging; SWIR; tissue optics

1 | INTRODUCTION

Contact dermatitis consists of the eruption of an often bothersome red, scaly, edematous and itchy rash resulting from skin exposure to a variety of compounds. Compounds that generate local skin toxicity cause irritant contact dermatitis (ICD). Alternatively, allergic contact dermatitis (ACD) is a delayed-type hypersensitivity reaction due to the reintroduction of compounds that a patient was sensitized to through prior exposure.^[1] While the well-known poison ivy induced rash such as shown in Figure 1 is an example of ACD, which often does not require medical intervention, contact dermatitis more broadly has been noted to be a disease with significant impact on public health.^[2]

The management of contact dermatitis consists first of accurate diagnosis, followed by avoidance of triggers and treatment of flares with both topical and systemic anti-inflammatory medications. In addition to complete medical history, physical examination and occasional skin biopsy for histopathologic analysis, diagnosis of contact dermatitis often involves the application and interpretation of a patch test. Patch testing^[3] represents the gold standard for both differentiation between ICD and ACD as well as for establishment of the causative agent eliciting the allergic reaction. Patch testing consists of applying multiple substances of interest to distinct areas of unaffected skin. The degree of inflammatory response to each applied patch testing substance is measured after several days by trained clinicians based upon qualitative clinical variables, including the degree of erythema, vesicle formation and induration. Given the qualitative nature of this measurement, significant limitations exist with regards to interobserver variability, particularly for mild or subtle cases of inflammatory response. Furthermore, accurate determination of erythema in patients with darker skin tones is more challenging.^[4] Given these challenges, a noninvasive quantitative

approach for the characterization of ACD that goes beyond visual inspection by a trained clinician would improve inter-rater reliability.

Hyperspectral imaging (HSI) has emerged as a powerful tool for investigating complex biological systems.^[5, 6] Unlike conventional imaging methods, each HSI pixel contains a full high-resolution spectral signal determined by individual chromophores and their interactions. Disease pathophysiology that leads to functional perturbations in tissue composition results in disease-specific variation in tissue chromophore distribution and intensity, which manifests as an alteration in the HSI-measured optical signal. These HSI-measured optical alterations are explored in a great variety of biomedical fields^[7, 8] including dermatology.^[9]

In this work, we applied short-wave infrared hyperspectral imaging (SWIR-HSI) to quantify ACD induced by poison ivy. It stands to reason that an imaging modality that enhances the signal from tissue water would be well suited for improved quantification of ACD. We therefore hypothesized that SWIR offers a more direct method for high contrast imaging of ACD, owing to several factors such as high sensitivity of SWIR to water, lower sensitivity of SWIR to melanin and hemoglobin (Hb), which are the main optical absorbers in the visible spectrum, and the lower scattering of tissue at longer wavelengths.^[10]

Our study aims at the development of a generalizable imaging approach for skin conditions, with an initial focus on ACD, using HSI in the SWIR. The current work is focused on the technical aspects of imaging and data analysis using a single clinical case to establish the utility of the method and provide initial testing of the approach. The major goals of this study were (a) directly visualize intralesional tissue fluid, and (b) optimize imaging parameters to provide high contrast quantitative SWIR-HSI lesion identification.

2 | MATERIALS AND METHODS/EXPERIMENTAL

2.1 | Patient information

Following a weekend of gardening, the subject, a 50-year-old Caucasian male, developed a linear collection of pruritic and erythematous oozing papules coalescing to plaques affecting bilateral ventral forearms. His characteristic rash and exposure history led to a diagnosis of ACD, likely urushiol-induced secondary to exposure to poison ivy or similar plants. The subject had no other evidence of skin disease or concerning cutaneous lesions. Between 7- and 26-days following exposure, and after informed consent was obtained, the subject's rash was assessed Mondays through Fridays with both a conventional visible range color camera and with a SWIR-HSI system. The test lab kept a stable temperature of 21°C to 23°C and stable relative humidity. Because of the possible fluctuations of water content during the day,^[11] the measurements were conducted at noon of each day. The protocol was approved by the Institutional Review Board at Washington University in St. Louis.

After complete resolution of the subject's primary rash, a control study was performed where 0.5 mL of sterile normal saline was injected intradermally to create a visible wheal in approximately the same area of the forearm previously affected by contact dermatitis.

2.2 | Color images

A Samsung Galaxy S7 cellphone visible camera was used to acquire red-green-blue color space (RGB) images. Per Samsung specifications, the camera utilizes a silicon-based Sony IMX260 sensor to cover the visible range.^[12] No additional image processing or rendering, except cropping, was performed on these color images.

2.3 | SWIR-HSI imaging system

The imaging HSI push broom data system (Figure 1) featured an SWIR sensitive 2D InGaAs thermoelectrically cooled CCD camera (Ninox, Raptor), a 25 mm focal length SWIR lens (StingRay Optics), an imaging spectrograph Inspector N17E (Specim), equipped with a 30 μm slit which provides 5 nm spectral resolution, and a linear, PC-controlled movable stage (Middleton Inc.). These components were integrated by Middleton Inc. into a stand-alone image acquisition system. Importantly, this system provided negligible chromatic aberration in the range of 600 to 1600 nm, thus eliminating a known problem in HSI.^[13, 14] To minimize specular reflection from the skin, the lens was appended with a SWIR polarizer (Boulder Optics) embedded in a rotating ring (Thorlabs). Two conventional incandescent 2×50 W halogen lamps (type Reveal, GE) with broad output from 400 to 2500 nm were used as the light sources.

The calibration of the system was performed using two laser lines: 1064 nm from the laser diode (Thorlabs) and 1550 nm (PolarOnyx). The laser lines were additionally verified using a spectrophotometer Nanolog equipped with an InGaAs linear diode array detector (Horiba).

2.4 | Spectral and image analysis

2.4.1 | Spectral analysis—The spectra extracted from the selected region of interest (ROIs) were preprocessed using multiplicative scattering correction^[15] where the average spectrum across the ROI was used as the reference. The new set of corrected spectra, including mean and corresponding SDs, was plotted using Origin 2019 software (OriginLab Corp.).

2.4.2 | SWIR-HSI image analysis—Data analysis of three-dimensional datasets (data cubes) from the hyperspectral system were performed using a built-in-house software IDCube on a MATLAB platform (version 2018b). (The software is available upon request.) The images were analyzed without the use of a reflection standard. ROIs corresponding to the affected and unaffected areas (ie lesion, unaffected skin, blood vessel) were selected, and the best contrast between the two ROIs as a function of the wavelength was identified. Contrast quantification algorithm between two ROIs was based on our published approach^[16] that uses Bhattacharyya distance D_b ^[17] as a metric of contrast. Briefly, the method is based on the assumption that each ROI is relatively uniform and represented by a single mode histogram representing pixel intensities. Two ROIs will therefore present a bimodal distribution, where the pixel intensities are clustered around two reasonably separated values. The range for D_b is from 0 (no separation between the modes of the image histogram, identical populations, and hence no contrast) to infinity (large separation, no overlap). Highly overlapped modes are characterized by low $D_b < 0.4$ to 0.5 and suggest a

low contrast with weak difference between the ROIs. Well separated modes with $D_b > 3$ would indicate a high contrast.

2.4.3 | Broadband image derived from SWIR-HSI—The acquired data cube was processed to generate a stack of 510 individual images corresponding to 510 wavelength channels equally dispersed in the range from 881 to 1710 nm with an increment of ~ 1.63 nm per channel. For the broadband image, all individual images were summed together to obtain a single monochromatic image. The assumption was made that the produced image is equivalent to the image taken by a broadband SWIR camera with no additional wavelength selection filter attached.

2.4.4 | Pseudo-RGB derived from SWIR-HSI—For the pseudo-RGB images, three wavelength channels at 1070, 1340 and 1605 nm were selected from the acquired data cube. The choice of these wavelengths was based on finding the best contrast between three distinct ROIs: the unaffected skin, the lesion and the blood vessel. For that, D_b values were computed for the set of ROIs and plotted against wavelength. Maximum D_b represents the higher contrast between the set of ROIs. The corresponding wavelengths were selected for the pseudo-RGB images. The image at the wavelength 1340 nm had the highest contrast between affected and unaffected skin. This wavelength was selected as a first channel. In the case of unaffected skin vs the blood vessels, the highest contrast was at 1070 nm with another prominent peak at 1340 nm. To avoid the overlap, 1070 nm was selected as a second wavelength. Finally, 1605 nm was selected as a third wavelength, which has the least overlap for the blood vessel and the affected skin. The three monochromatic images of the selected wavelength were assembled to form a three-band RGB image with the red channel corresponding to 1070 nm, green channel to 1340 nm and blue channel to 1605 nm. For visualization, the constructed pseudo-RGB image was remapped to the range of 0 to 1 with higher value corresponding to a higher photon intensity. These three wavelengths were used to generate pseudo-RGB images for both the control intradermal saline study as well as ACD lesion analysis.

2.4.5 | Tissue fluid index (TFI) derived image—To visualize lesional skin more clearly, we applied a normalization to each channel from the pseudo-RGB image. Specifically, for each pixel of the image, the R, G and B channel intensities were divided by the average R, G and B intensities of adjacent unaffected skin. This normalization can be represented by the following Equation (1):

$$\text{TFI Image} = [R, G, B] = \left[\frac{R_{(1070)}}{R_{U(1070)}}, \frac{G_{(1340)}}{G_{U(1340)}}, \frac{B_{(1605)}}{B_{U(1605)}} \right] \quad (1)$$

where R , G and B are the intensities at the red, green and blue channels at a given pixel of the pseudo-RGB image, respectively, and R_U , G_U and B_U are the average intensity values of unaffected skin from the red, green and blue channels, respectively.

The normalized individual monochromatic images were then assembled to form a color RGB image representing a TFI-derived image. The relative increase in lesional fluid content compared to unaffected skin was quantified by computing the TFI, defined by Equation (2):

$$TFI = \frac{(I_S - I_U)}{I_S} = \frac{\text{mean}(I_R, I_G, I_B)_S - \text{mean}(I_R, I_G, I_B)_U}{\text{mean}(I_R, I_G, I_B)_S} \quad (2)$$

where I_S is the average (mean) intensity of affected skin from all three R,G,B channels in the derived TFI image, and I_U is the average intensity from all three R,G,B channels of the unaffected region from the TFI image.

As is evident, TFI index has a range from 0 to 1, with 0 corresponding to baseline tissue fluid content of unaffected skin and 1 corresponding to the limit where lesional fluid content is much greater than the fluid content of unaffected skin.

2.4.6 | Tissue erythema index—Tissue Erythema Index (TEI) was derived from the RGB images recorded by the color camera to measure the redness and quantify erythema. The formula for measuring TEI is similar to TFI and is defined by Equation (3):

$$TEI = \frac{I_S - I_U}{I_S} = \frac{\text{mean}(I_R, I_G, I_B)_S - \text{mean}(I_R, I_G, I_B)_U}{\text{mean}(I_R, I_G, I_B)_S} \quad (3)$$

where I_S is the average (mean) intensity of affected skin from all three R,G,B channels in the RGB image, and I_U is the average intensity from all three R,G,B channels of the unaffected region.

Similar to the TFI, TEI has a range from 0 to 1, with 0 corresponding to baseline tissue redness content of unaffected skin and 1 corresponding to the limit with the highest redness.

3 | RESULTS

3.1 | Water shows strong contrast in SWIR

Since ACD demonstrates increased fluid histologically, we first explored the imaging of a drop of water under SWIR-HSI conditions. A water drop was placed in a cup made from Spectralon (Figure 2), a fluoropolymer, which has high diffuse reflectance over a broad including SWIR spectral range^[18] and imaged using a push broom SWIR HSI system. Because water has very weak absorption in the visible spectral range, it appears colorless (Figure 2A). Due to the increased absorption in SWIR, at certain wavelengths water becomes chromogenic as illustrated by Figure 2B, where water appears orange (pseudo-RGB at 1070, 1340 and 1605 nm), while the Spectralon cap remains white due to the lack of any absorption bands. The reflection spectra of water and Spectralon are shown in Figure 2C.

3.2 | SWIR-HSI enables identification of intradermal water accumulation

Normal saline solution injected intradermally in an otherwise healthy appearing region of the subject's forearm immediately resulted in formation of a small (0.8 cm diameter) wheal that almost completely disappeared 30 minutes after the injection. In the color image acquired from a color camera (Figure 3A), the saline induced edematous wheal is poorly distinguished from adjacent normal skin. This poor contrast is due to the low absorption coefficient of water (less than 10^{-1} cm^{-1}) in the visible range. In SWIR, water has higher

absorption coefficient in the range of 5×10^{-1} to 10^2 cm^{-1} ,^[19] thus enabling the distinction of biological tissues based on their water content. Indeed, both a broadband SWIR image (Figure 3B) and a pseudo-RGB image derived from SWIR-HSI (see Supplementary Methods), presented clear visual evidence of the saline injection site (Figure 3C). The bright red-colored area corresponds to the edematous wheal and attests to dermal accumulation of water.

The reflectance spectra of the unaffected skin adjacent to the injection site (Figure 3D) presents several well-defined features that are consistent with the published skin reflectance measurements.^[20] Within the SWIR spectral range, relatively high reflection in the range from 1000 to 1350 nm is due to the relatively low absorptivity of water, lipids, melanin and proteins^[19, 21] that constitutes the chemical composition of the skin. The presence of dermal saline immediately after its subcutaneous injection decreases the reflection intensity. This lower intensity is attributed to the increased level of water absorbing in the SWIR range and, to a lesser degree, the reduction in scatterer density within the edematous dermis.^[22]

3.2.1 | Spectral analysis of lesional skin with SWIR-HSI confirms increased intralesional water content—The spectral changes in ACD lesional area were similar to those observed in the saline-injected skin (Figure 4A). The difference between the spectrum of the lesion and the adjacent unaffected tissue was close to the spectrum of water (compare Figure 2C and Figure 4B). The similarity between the saline injected and the lesion can be further illustrated by comparing skin spectra normalized to healthy skin showing almost complete overlap (Figure 4C).

3.2.2 | Contrast in broadband—SWIR—We next investigated the contrast between the ROIs from the data produced by the SWIR-HSI system. This imaging system generates images from 510 wavelength channels that can either be treated individually or combined. An image from the sum of all channels from 881 to 1710 nm is equivalent to the image taken by a broadband SWIR camera. These broadband SWIR images for each day of imaging are shown in Figure S2. Visual analysis of the images suggested a sufficient contrast between the areas of interest up to Day 9. Starting from the Day 10, the lesional area was difficult to distinguish from unaffected skin, similar to the visible range color camera.

Quantitative analysis of these images was achieved using Bhattacharya distance D_b ,^[16] which we applied to calculate the contrast between the affected and unaffected areas of the skin (Figure 5A). Higher D_b indicates better contrast. Indeed, D_b is >1.0 from Day 1 to Day 9, where the lesion was visually distinguishable from unaffected skin using broadband SWIR. In the subsequent days where visual contrast is poor, D_b is <0.4 ($D_b = 0.36$ on the Day 10 and $D_b = 0.04$ on the Day 19).

3.2.3 | Visual contrast in SWIR-HSI can be improved at 1340 nm—Visual contrast can be improved by generating images from specific wavelengths, where signal variation is high, rather than summing the signal at all wavelengths. The highest contrast between the two ROIs can be achieved at 1340 nm (Figure 5B). The images at 1340 nm are shown in Figure S3 with the lesion more easily distinguishable from adjacent unaffected

skin even in last few days of imaging. The intensity of the contrast ranged from $D_b \sim 7$ on the first day of imaging to $D_b \sim 0.42$ on the Day 15 (Figure 5A). For comparison, the contrasts in the broadband images from the same ROIs were significantly lower and ranged from $D_b \sim 2.5$ on Day 1 to less than 0.05 on Day 19.

3.2.4 | Pseudo-RGB models improve the perception of the lesion—While monochromatic images are preferred for quantification, color images are better for visual perception.^[23] The most common color space is based on RGB, which is an additive color model where the red, green and blue channels are combined together.^[24] Similar color space can be arranged in other spectral ranges, where any three given wavelengths can be added together to generate a pseudo-RGB model.

Identifying the best set of three wavelengths to produce the optimal image is challenging in SWIR-HSI since the number of individual combinations is rather high, >22 million for our 510-channel system. The choice of the three wavelengths was based on the selection of three distinct ROIs: the lesion, the unaffected skin and the blood vessel (Figure S4A, also see “Methods” section in Data S1 that describes the selection of wavelengths). The contrast between the pairs of ROIs was expressed as Bhattacharya distance and plotted against the wavelength (Figure S4B). The highest contrast between the affected and the unaffected skin was at 1340 nm (vide supra). We selected this as the first channel. The highest contrast of unaffected skin vs blood vessels was at 1070 nm. The blood vessel vs affected skin contrast plot showed several peaks at 920, 1070, 1350 and 1605 nm reflecting a complex composition of chromophores. We selected 1605 nm as a third channel due to low overlap with other selected channels. The 1070 nm channel was assigned as red, 1340 nm as green and 1605 nm as blue.

The resulting pseudo RGB-type SWIR images shown in Figure 6 substantially improved the perceived contrast compared to the monochromatic images. Unlike the visible range, broadband, or 1340 nm SWIR images, the pseudo-RGB image’s lesional affected areas are visibly distinguishable from the unaffected skin on every day of imaging, including the last day.

3.2.5 | Tissue fluid index (TFI) quantifies lesional fluid content—The TFI quantifies the relative increase in tissue fluid content compared to unaffected skin. Since ACD is pathophysiologically characterized by increased water content between epidermal skin cells, the TFI is a useful quantitative measure of the degree of this allergic reaction. Equation (1) was used to construct the pseudo-RGB allergic inflammation index image (Figure 7A), and the numerical index value was computed from the resultant image using Equation (2). The index value ranges from 0 to 1 where higher values indicate more significant tissue fluid content. Threshold value of 0.02 was obtained by taking the average of the TFI value computed from a region of adjacent unaffected skin.

3.3 | Color images from conventional visible range camera

ACD has a specific visual appearance consisting of varying degrees of skin redness, scaling, oozing and swelling. These characteristic skin findings serve as a visual analogue of the skin’s inflammatory response to specific ACD triggers, but are not direct measures of the

pathophysiology driving ACD. Nevertheless, clinicians typically rely upon visual assessment alone to determine the degree of inflammation. We therefore first evaluated the subject's poison ivy rash using a conventional visible range camera. On the first day of imaging, the rash is easily visualized as an erythematous and edematous plaque (Figure 1). On Day 2, the rash appears to be progressing and affecting a larger area. Over the remaining week of imaging (Day 3-Day 7) the rash gradually fades, with decreasing erythema and apparent flattening of the lesion. By the end of the second week (Day 10-Day 15) the affected area and background, unaffected skin become difficult to distinguish. On Day 19 a faint erythematous patch, nearly indistinguishable from adjacent unaffected skin, remains.

Color visible images are often used for quantification of skin erythema.^[25] We used a TEI derived from color visible images to quantify erythema. Figure 8 shows that FEI appears to be indistinguishable for the first 11 days, and after which, the signal appears to be decreased. It is clear from this data that FEI gives relatively low dynamic range with the value (0.01-0.22 on a scale between 0 and 1) with a lack of a clear monotonic trend. In contrast, TFI derived from SWIR images (Figure 7D) demonstrated a much higher dynamic range (0.02-0.5 on the same scale between 0 and 1) with monotonic linear decrease corresponding to resolution of clinical rash. This comparison suggests higher sensitivity of the SWIR-based TFI index compared to the visible range TEI to quantify ACD and supports that the accumulation of fluid is a useful marker of ACD. Furthermore, the poor correlation between TEI and TFI from Day 1 to Day 11 (Pearson coefficient = 0.37 and $R^2 = 0.14$, Figure S5) and, no correlation from Day 1 to Day 10 (Pearson coefficient = -0.02) supports the assertion that increased local blood content is not a hallmark of ACD. The poor correlation between TEI and TFI is not unexpected when one considers the pathophysiology of ACD. While an influx of immune cells associated with local inflammation would be predictable, ACD is not driven pathophysiologically by increased local blood content. Instead, a tissue biopsy of ACD typically reveals a characteristic spongiosis feature in the epidermal layer. In the setting of spongiosis, the normally closely packed keratinocytes are spaced apart due to increased tissue fluid. Desmosomes are present between keratinocytes but difficult to visualize in unaffected skin. However, similar to rebar becoming visible when bricks of a reinforced concrete wall are pulled away from each other, desmosomes become recognizable as keratinocytes are pushed apart by increased fluid volume. It is precisely this increased fluid volume that HSI in the SWIR directly detects.

4 | DISCUSSION

The optical properties of skin are important monitoring and predictive parameters for dermatologic lesions.^[26, 27] Until relatively recently, visible changes in skin morphology, color, texture and spatial distribution discernable to the human eye have been the only available indicators to identify skin abnormalities.^[28-30] A number of descriptors derived from these visual observations provided qualitative metrics, such as numeric grades, for skin evaluation. These grades can be either inconsistent, as they rely upon the experience of the observer, or of low sensitivity, due to suboptimal wavelengths selection. To improve the diagnostics, a toolbox of optical spectroscopic methods capable of measuring skin parameters such as absorption and scattering coefficients, levels of Hb,^[31] and arrangement of keratin fibers have been evaluated.^[32]

The qualitative and subjective nature of skin interpretation has led to several groups exploring noninvasive imaging modalities that can help more rigorously and quantitatively assess contact dermatitis and similar skin conditions. Alda et al applied Raman spectroscopy to identify nickel allergy.^[33] Gonzalez and his colleagues utilized reflectance confocal microscopy to image skin after patch testing.^[34] Boone et al demonstrated that high-definition optical coherence tomography is useful in differentiating irritant from ACD.^[35] Huck et al developed fluorescence lifetime imaging modality combined with multiphoton-based intravital tomography to investigate atopic dermatitis in patients.^[36] More recently, Anzengruber et al proposed using a FLIR thermal camera to quantitatively measure ACD dermatitis and distinguish it from ICD.^[37]

Spectral analysis of the light reflected from the skin surface can be used to extract information regarding skin chromophore concentration and distribution^[23, 28, 29, 32, 38] and represents an additional noninvasive imaging modality with exciting applications in dermatology. For example, a commercially available imaging system for spectrophotometric intracutaneous analysis obtains skin lesion images at eight wavelengths between 400 and 1000 nm, and, with the aid of spectral analysis, quantifies the amount and distribution of melanin, Hb and collagen within the lesion.^[39] Stamatas et al proposed a method for noninvasive in vivo quantification of edema by a spectral imaging technique that leveraged the characteristic absorption bands of Hb and water in the visible and near-infrared (NIR), up to 970 nm, and validated this method in a histamine-induced cutaneous edema model.^[22] Nishino et al used HSI in the infrared from 1000 to 2400 nm to develop a spectral-based classifier that could distinguish between normal skin, type I urticarial reactions and type IV hypersensitivity reactions.^[20]

The core notion of the presented work is to approach a common skin condition in a more mechanistic way guided by an understanding of the pathophysiology behind the disease with an imaging tool. An important distinction of our approach is to generate enhanced visual contrast by identification of specific wavelengths with which to generate high contrast pseudo-RGB images and our ability to quantify the relative increase in lesional tissue fluid accumulation compared to background unaffected skin. The results clearly demonstrate enhanced lesional tissue fluid accumulation consistent with the spectral signal obtained from an intradermal saline control. The initial insight that inspired this study is the increased tissue fluid in the superficial layer of skin often seen in histology of ACD. Clinical observation by eye, or with a visible camera, relies on observing redness, scale and vesiculation, which are surrogate markers for the underlying pathophysiology driving contact dermatitis. A hyperspectral approach in the Vis range may yield some combination of wavelengths that also boosts signal to noise, but the disadvantage of that is those wavelengths would not a priori be connected to the underlying physiology of this disease entity. As we have demonstrated, hyperspectral SWIR imaging is well suited to directly measure tissue fluid content. The benefit of the SWIR spectral range is that chromophores with low absorption coefficients in the visible range, such as lipids and water, have much higher absorption coefficients in SWIR.^[10, 27, 40] At the same time, melanin one of the major absorbers in the visible range has relatively weak absorption in SWIR.^[41] These two factors make SWIR unique and somewhat more suitable for diagnosing dermatological problems and may be especially useful in people with darker skin.

We applied SWIR spectral range because ACD is characterized pathophysiologically by increased epidermal fluid accumulation. With water being the major component, this increased fluid is essentially invisible in the visible range because of the low absorption of water between 400 and 700 nm. The high absorption of water at around 1400 nm makes the SWIR range more suitable for directly assessing tissue fluid content. Indeed, by combining SWIR with HSI, we found that the spectral signature of intradermal saline to be nearly identical to ACD, which further demonstrates the ability of SWIR-HSI to visualize tissue fluid content.

The advantage of SWIR-HSI in skin diagnostics can be appreciated by considering how light propagates through tissue. Light that is not reflected directly from the surface passes through a melanin rich epidermis and an upper dermis with a plexus of blood vessels before interacting with collagen in the lower dermis.^[42] This model, shown in Figure 9, highlights the human tissue chromophores that influence the spectral measurement of skin disease: melanin, Hb, oxyhemoglobin (oxyHb), water and lipids. Melanin absorbs quite strongly in the visible range^[38] with diminishing absorption beyond 1400 nm, limiting light penetration to the epidermis within the visible range. Hemoglobin (both Hb and oxyHb) absorbs strongly across the entire visible and NIR range. Depth of penetration increases within the NIR, 700 to 900 nm spectral range, allowing for visualization of blood vessels through the melanin layer. In the absence of disease, any visible light that penetrates deeper into the dermis will interact with lipids and water, which have low molar absorptivity in the visible range. Therefore, the deeper dermis can be considered an essentially chromophore-free region with respect to the visible range. In the SWIR range however, lower absorption coefficients of melanin, Hb and oxyHb substantially lowers scattering^[28] and results in deeper light propagation. Concomitant with this deeper light propagation, the increased absorption coefficient of water and lipids in the SWIR range turn these invisible components into powerful chromophores, thereby turning the dermis into a chromophore rich area with respect to the SWIR.

Because our approach is able to more directly assess the increase in tissue fluid content associated with the characteristic pathophysiologic changes seen in ACD, we suspect that it would offer a novel and effective approach towards improved patch test quantification. Specifically, the use of the TFI can quantify the degree of tissue fluid accumulation across multiple patch test results, allowing for a more robust approach towards patch test reading. As mentioned in Introduction, contact dermatitis is divided into ICD, where an irritant directly causes cellular damage, and ACD, where an immune response to a substance generates a skin eruption. Proper clinical management relies on differentiating between these two forms of contact dermatitis, and because of overlapping histological features on biopsy, patch testing remains the gold standard for making this determination.^[3] While spongiosis is a histological feature that is shared between ACD and ICD, ACD may show greater degrees of intercellular edema, which we would expect to result in a greater degree of HSI detected tissue fluid content present in ACD compared to ICD.^[43] In addition, by allowing imaging of large areas at one time, HSI may provide a novel approach towards patch test quantification—thereby standardizing and improving upon the current gold standard. Furthermore, because melanin has lower absorption in the SWIR range than in the visible range, SWIR-HSI imaging should be relatively independent of skin tone, thereby making it

potentially easier to distinguish erythema in patients with darker skin tones, something that can be challenging by clinical examination alone.^[44] Further studies must be done, however on subjects with darker skin tone to verify this potential utility. Finally, because we have identified three SWIR wavelengths that maximize contrast, a modified device that only acquires imaging data from these specific wavelengths may be an affordable and faster imaging modality relevant to diseases like ACD where tissue fluid content is altered.

The current study focuses on the imaging spectroscopy and imaging algorithms applied to human tissue. We demonstrate that SWIR-HSI method is a promising imaging modality in quantitative detection of water-based fluid under the skin. While the current study demonstrates the suitability of our approach to identify quantitative parameters in skin, and demonstrates an impressive signal linearity over time with disease resolution, it is early to generalize the conclusions to diagnostics of ACD or any other skin pathologies. The current results are aimed at providing technical details with a single patient to serve as a proof of principle example. Though the validity of the results is strengthened by the approach being motivated by disease physiology, further studies demonstrating the repeatability of the proposed imaging algorithm in a larger patient population, including patients with different age, sex and skin pigmentation will be needed to verify the approach and demonstrate its clinical utility.

5 | CONCLUSIONS

The potential of HSI in SWIR-HSI, spectral range 880 to 1700 nm, was evaluated for diagnosing and monitoring ACD in a subject with poison ivy dermatitis. This approach provided direct noninvasive evidence of the aqueous nature of fluid retained in the lesion area, consistent with the pathophysiology of ACD. Higher contrast between the affected and healthy skin, using Bhattacharyya distance as a metric of contrast, was achieved through a selection of specific wavelengths at 1070, 1340 and 1605 nm and combining them in a pseudo-RGB. This SWIR-HSI approach along with image processing, enabled visualization of the lesion at significantly later stages as compare to the conventional color camera in the visible range. Based on this imaging data, a new TFI, where the pseudo RGB image of the lesion is normalized to unaffected skin, is proposed to further enhance contrast between the lesion and unaffected skin. Overall, the proposed SWIR-HSI approach provided insight into pathophysiology of the lesion by directly measuring the increased fluid content associated with the ACD rash, enabling more accurate diagnosis and monitoring of the lesion. The current study based on a single case demonstrate the suitability of our approach and the workflow to identify quantitative parameters in ACD using HSI in the SWIR spectral range. A large patient population with diverse types of skin will be needed to validate the approach and demonstrate its clinical utility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ACD	allergic contact dermatitis
Hb	hemoglobin
HSI	hyperspectral imaging
ICD	irritant contact dermatitis
oxyHb	oxyhemoglobin
RGB	red-green-blue color space
ROI	region of interest
SWIR	short-wave infrared
TEI	tissue erythema index
TFI	tissue fluid index

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FIGURE 1.

Color images of the poison ivy lesion made by conventional color camera. On the first day of imaging, the rash is easily visualized as an erythematous and edematous plaque. The images show weak contrast between the lesion and the healthy skin after Day 10

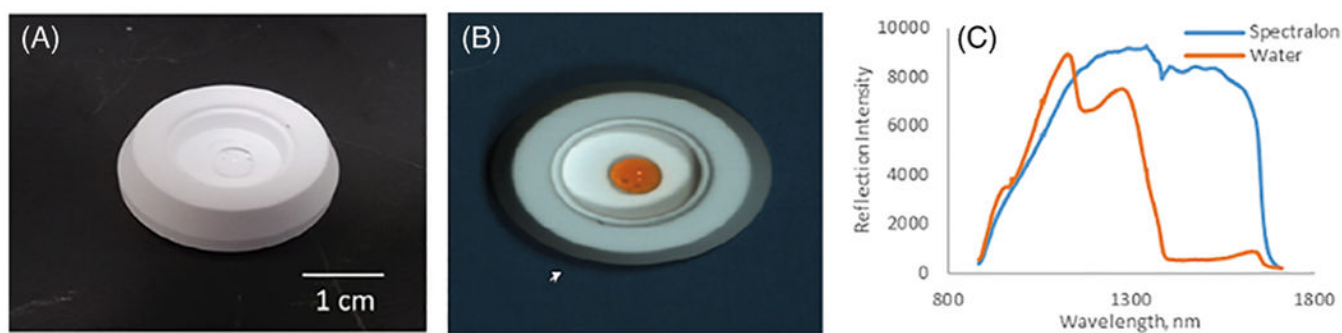


FIGURE 2.

Imaging of water. A, Image of a water droplet in a Spectralon cap using a Samsung color camera. B, Imaging of water using SWIR-HSI, pseudo-RGB at 1070, 1340 and 1605 nm. C, The reflection spectra of water and Spectralon under the SWIR-HSI conditions. The spectra were not corrected for the light source

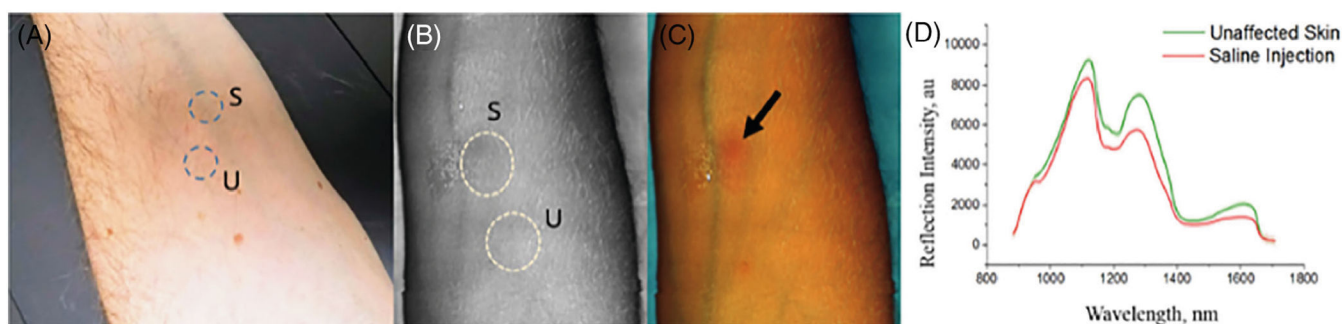


FIGURE 3.

Imaging of saline-injected skin. A, Color image acquired by a Samsung cellphone camera. ROIs corresponds to saline injected (S) and unaffected skin (U). B, Broadband SWIR image. C, Color image from SWIR-HSI in pseudo-RGB 1070, 1340 and 1605 nm; arrow shows the location of the saline injection. D, Mean SWIR spectra of the ROIs

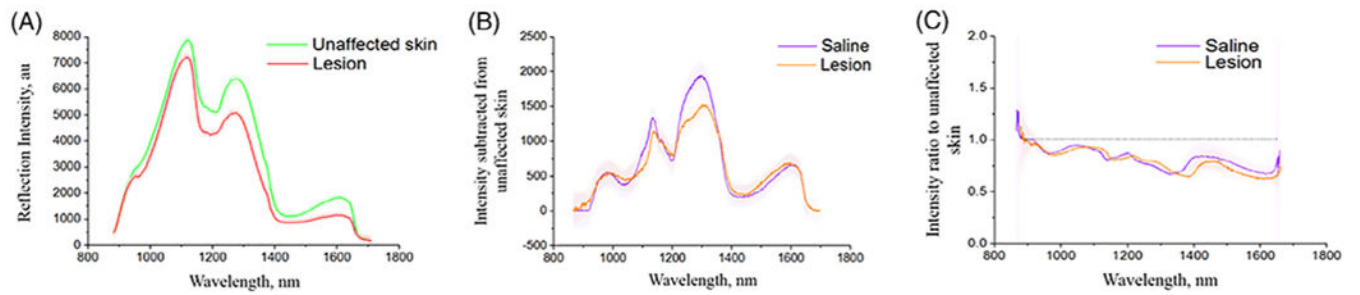


FIGURE 4.

Poison ivy lesion vs saline injection. A, Mean SWIR spectra of the lesion and unaffected skin. B, Intensity subtraction spectra: saline—unaffected skin and lesion—unaffected skin. C, Normalized spectra: the spectra present as normalized to unaffected skin. A horizontal line at $y = 1$ corresponds to the ideal case where the two ROIs have identical optical properties. All spectra are shown with SDs

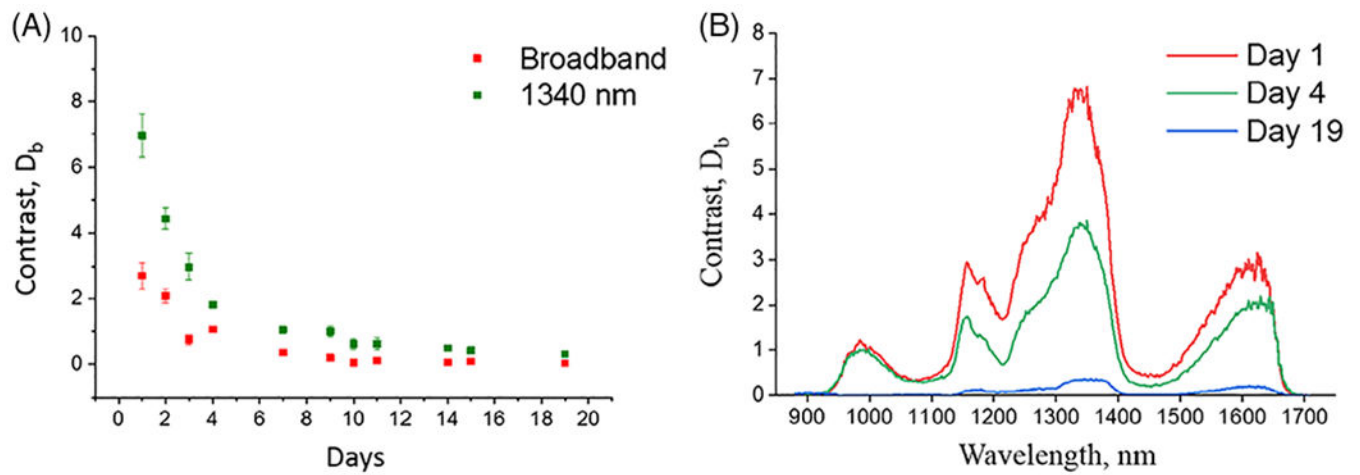


FIGURE 5.

Contrast between lesional and unaffected skin areas measured using Bhattacharya distance.

A, Longitudinal change of the contrast at 1340 nm. Error bars correspond to one SD

between several ROIs. B, The highest contrast between the lesion and the unaffected skin.

This highest contrast at 1340 nm is maintained through the entire imaging time (Day 1-Day 19)

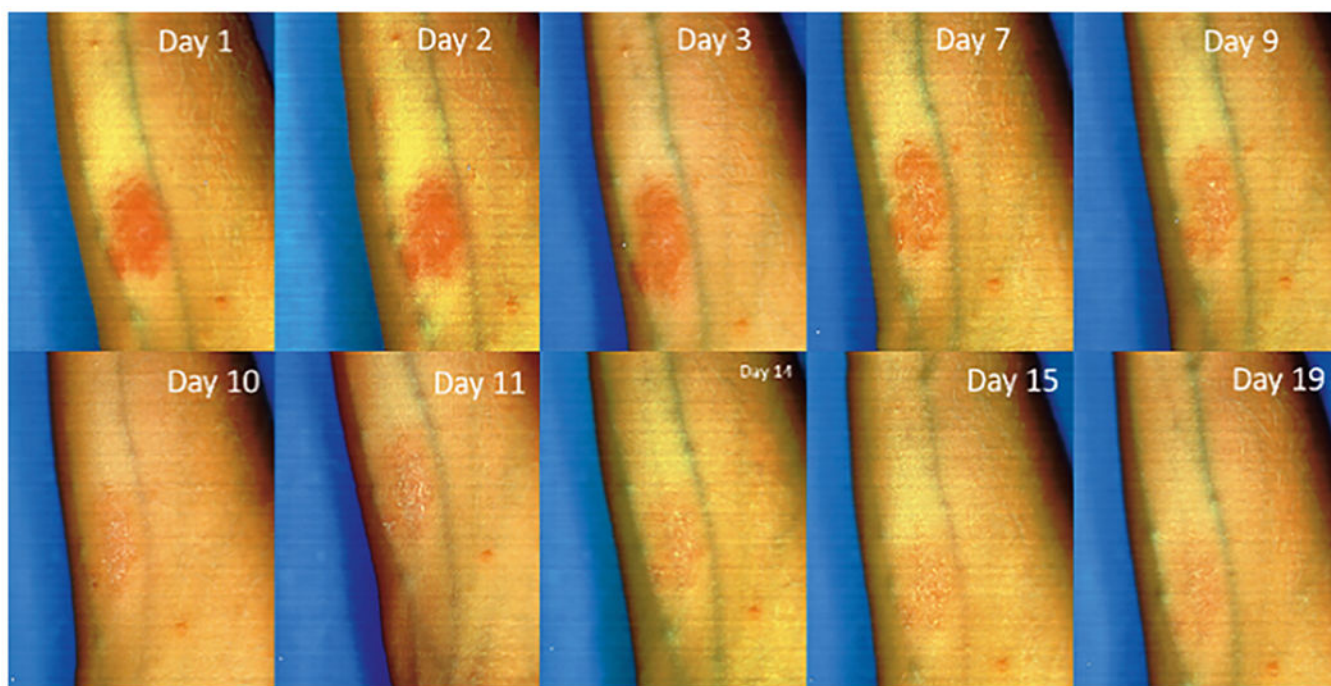


FIGURE 6. SWIR-HSI images in pseudo-RGB images. Derived from a set of three wavelengths (1070, 1340 and 1605 nm) for Day 1 to Day 19

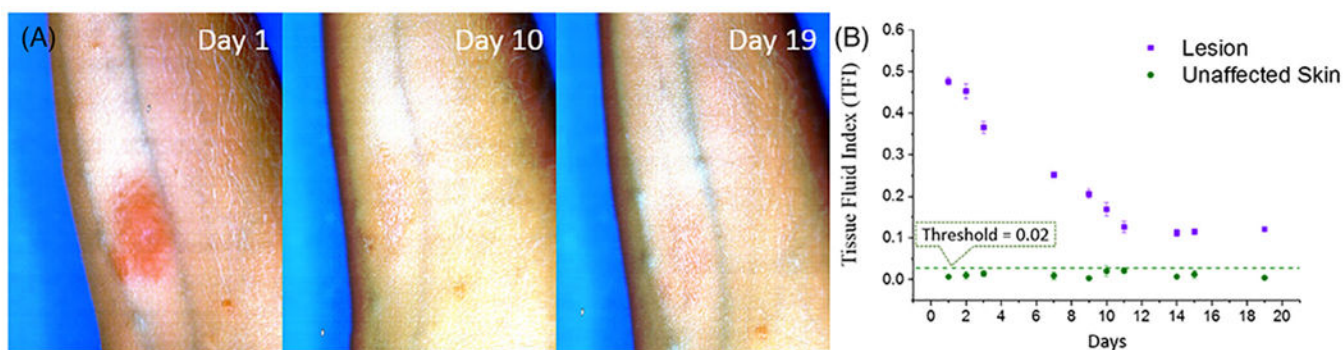


FIGURE 7.

Tissue fluid index, A, images derived from Equation (1); B, quantitative tissue fluid index computed using Equation (2) for Day 1 to Day 19

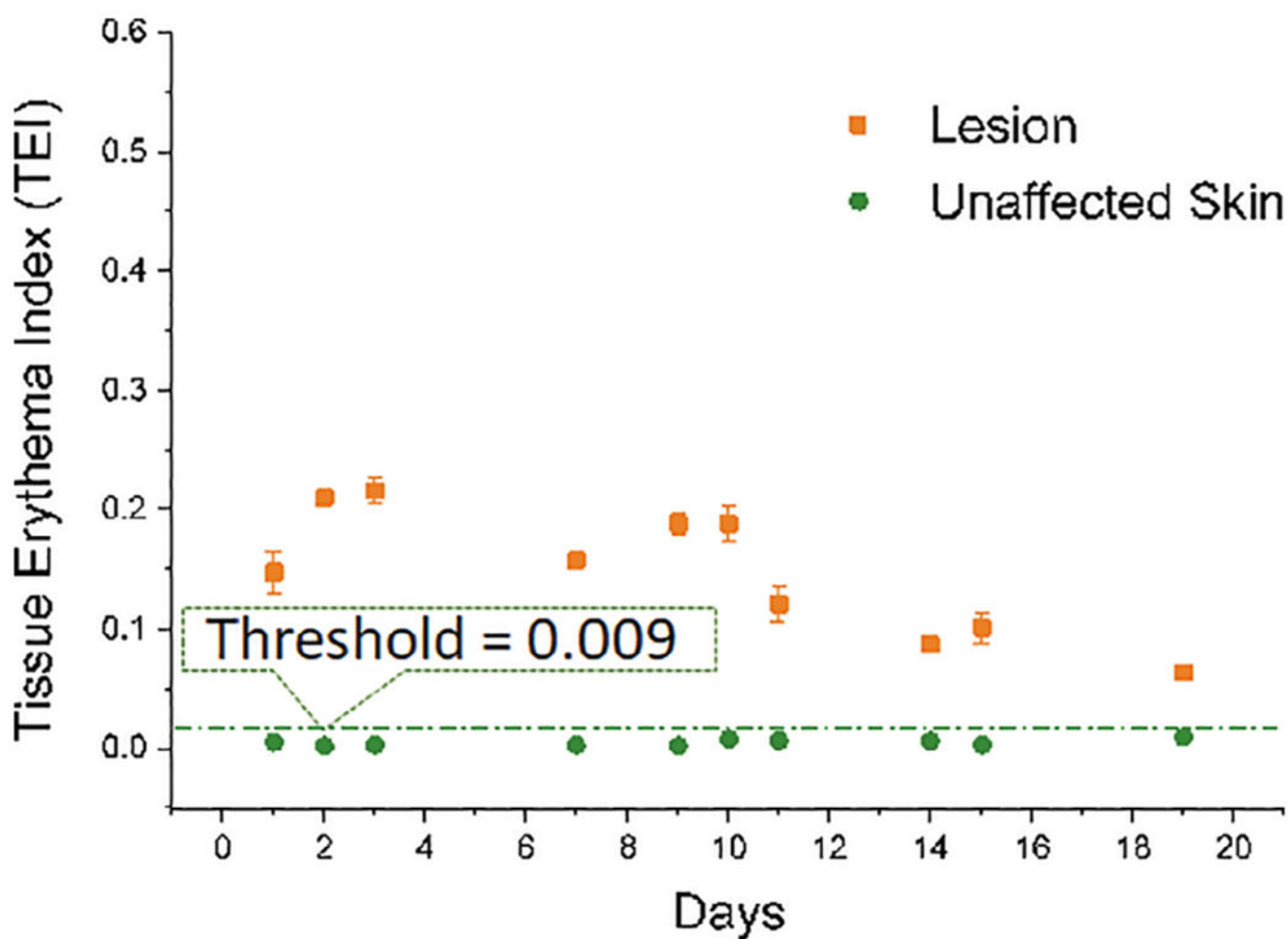


FIGURE 8.

Tissue erythema index derived from the color Vis images measures quantifies erythema

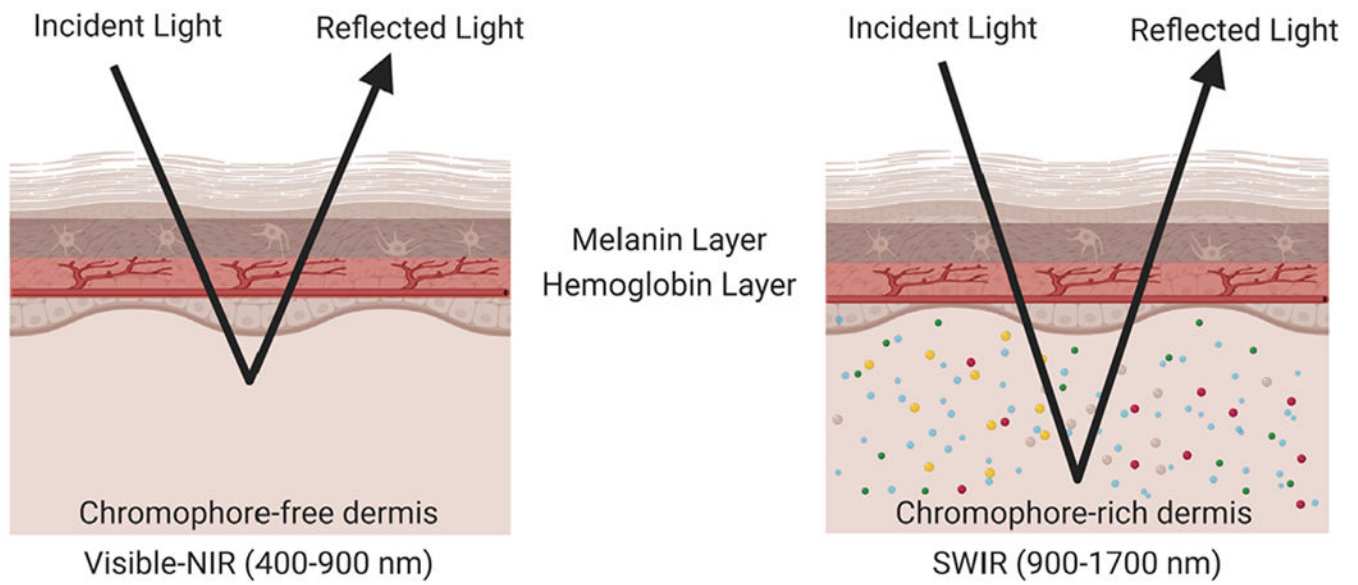


FIGURE 9.

Anatomical model of the visible and SWIR photons penetrating through the skin.

Chromophore-free dermis under Vis-NIR range turns into chromophore-rich tissue under the SWIR illumination